Research Proposal Form of the Thesis Entitled

Estimation of Soluble Urokinase Plasminogen Activator Receptor Levels in Peri-implant Crevicular Fluid For Evaluation of Peri-implant Mucositis and Peri-implantitis

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Introduction

Teeth loss can occur due to many factors and surgical implants are one method of rehabilitation. As implants become increasingly widespread, the occurrence of associated complications increases as well. Mayfield and Salvi described peri-implant mucositis as an inflammatory lesion of the mucosa around an endosseous implant that will not result in the destruction of underlying bone or continued marginal bone loss (Heitz-Mayfield & Salvi, 2018). On the other hand, Schwarz and associates described peri-implantitis (PI) as a pathogenic disorder that affects the connective tissue surrounding dental implants resulting in inflammation of connective tissues and continuous bone resorption (Schwarz et al., 2018). In a meta-analysis and systematic review by Derks and Tomasi, it was observed that the overall prevalence of peri-implantitis was 22 %, and peri-implant mucositis was 43 % (Derks & Tomasi, 2015). The absence of clinical symptoms of inflammation around the implant is referred to as peri-implant health (Araujo & Lindhe, 2018; Renvert et al., 2018).

There have been observations regarding anatomical variations in the mucosa around an implant and periodontal tissues. In contrast to the periodontium's perpendicularly oriented fibres, collagen fibrils in peri-implant tissues are parallel in orientation. Additionally, fibres apical to the junctional epithelium are more collagenous, less vascular, and contain less fibroblast content, all of which may threaten the survival of dental implants to inflammation (Berglundh et al., 1991, 1994). Early detection of any inflammatory changes around Dental implant helps to prevent and cure peri-implant diseases. PICF/GCF has considerable potential to reflect inflammatory alterations and tissue loss because of the content and volumetric changes it undergoes during inflammation (Güncü et al., 2009, 2012).

Owing to the complexity of diagnosing PID and its rate of progression, biomarker analysis may facilitate in the early detection of peri implant diseases. In addition, they can also be utilized for the staging and grading of periodontal inflammation (Tonetti et al., 2018).

It is likely that crevicular fluid of peri-implant tissue comprises biological marker that can aid in the detection and forecast of future disease, allowing for the development of an especially effective treatment strategy. In medicine, a biomarker is a parameter that has been objectively studied and

evaluated as a predictor of normal biological, pathological, or therapeutic intervention response (Strimbu & Tavel, 2010).

In the urokinase-type plasminogen activator system, there is an enzyme possessing proteolytic functions that also serves as a receptor (uPAR), alongside inhibitors. Roldan and associates (Roldan et al., 1990) replicated uPAR , and Ploug and coworkers discovered its soluble form (suPAR) (Ploug et al., 1991). Cell surface urokinase-type plasminogen activator receptors (uPARs) are connected to immune cells (including PMNs) via a anchor named as glycol-phosphatidyl-inositol. uPARs regulate extracellular cell migration, adhesion, and chemotaxis through a variety of molecular interactions with vitronectin, uPA, and integrins. When PMNs are activated, uPAR is cleaved from the cell membrane, allowing for the entry of soluble urokinase-type plasminogen activator receptor (suPAR) into the gingival crevice and eventually into the saliva (Blasi & Carmeliet, 2002).

The soluble urokinase-type plasminogen activator receptor (D1–D3) has three domains (D1, D2, and D3). SuPAR has two free domains: D1 and D2–3. The circulation possesses all three suPAR molecular variants. A chemotactic sequence in the D2–D3 fragment binds to formyl peptide receptors, attracting other immune cells to the inflammatory region (Pliyev & Menshikov, 2010). SuPAR's molecular stability in bodily fluids makes it a preferred biomarker for systemic inflammation. SuPAR can be found in blood, plasma, serum, urine, pleural fluid, peritoneal, and CSF (Huai et al., 2006; Ostergaard et al., 2004; Senoo et al., 2010). SuPAR levels in the blood have been discovered to be elevated in a range of illnesses, including cancer, cardiovascular disease, and diabetes, to mention a few (Thun. et al., 2009). Plasma suPAR has the advantage of increasing in systemic inflammation but has the disadvantage of not increasing to a specific clinical state.

To the best of my knowledge, no clinical application of PICF for measuring suPAR levels in peri-implant diseases has been described yet. So, the intent of this study was to look at the amounts of suPAR in PICF at both healthy and problematic implant sites. It was also intended to test the scientific reliability of suPAR as an indicator of disease and investigate the relationships between parameters such as clinical and biochemical.

Review of Literature

Skottrup and his team studied the function of suPAR as an indicator of systemic inflammation. Adolescents suPAR levels were compared to salivary suPAR levels to assess their relationship to periodontal problems. Saliva, serum, and subgingival plaque samples were taken from adolescents who reported diagnosed with periodontitis (n = 87) or without periodontitis (n = 73). The immersion of suPAR in saliva and serum were quantified, together with the immunoglobulin specificity towards 18 different bacteria species. The number of variables in the clinical, microbiological, and immunological categories were reduced by component analysis. It was discovered that salivary suPAR values were indifferent to serum suPAR values. The concentration of suPAR in saliva was inter related with the clinical features of 'Periodontitis Extent' (b = 0.28) and 'Putative periodontal pathogenic' (b = 0.65). This study is the initial one to assess suPAR levels in saliva among a wider teenage population. Their results indicate that suPAR in saliva could be used clinically as an inflammatory periodontitis biomarker (Skottrup et al., 2018).

Taşdemir and colleagues assessed the concentrations of suPAR activity and galectin-1 in GCF and saliva. They split the 60 volunteers into different categories: such as Group P which includes chronic periodontitis ,Group G which includes gingivitis, and Group H which includes healthy periodontal and each group had 20 patients. Their aim was to determine the significance of these molecules in the inflammation of the periodontium. Researchers used the ELISA method to look at the samples and found that people with periodontal disease had higher amounts of suPAR in Saliva as well as Galectin 1 and suPAR in GCF. This suggests that these substances may be involved in periodontal inflammation. SuPAR and galectin-1 could also serve as diagnostic indicators for periodontal disease (Taşdemir et al., 2020).

Isola and colleagues evaluated the suPAR level in saliva and blood serum can be altered by influence of gingival inflammation, periodontal inflammation, and ischaemic heart disease, with the goal of developing suPAR as an indicator for periodontitis and ischaemic heart disease. In this study, healthy there were 33 healthy patients in control group patients and 31 patients with Periodontitis, patients

with coronary artery disease (n=29), and patients with a combination of periodontitis and coronary artery disease (n=29) were recruited. All individuals underwent clinical and periodontal evaluations, as well as frequent blood tests for serum lipids, h-CRP, and plasma and salivary suPAR levels. The analysis revealed that patients with periodontitis and periodontitis + CHD had higher suPAR levels in both plasma and saliva than healthy controls and CHD (Isola et al., 2021).

Alshiddi and colleagues demonstrated a association between the levels of suPAR, galactin-1, and IL-1, and periimplant diseases. The study sought to evaluate the amounts of Interleukin-1, suPAR and galectin-1, in PISF throughout periimplant mucositis(PIM) and periimplantitis. From the patients' dental records, information about the patients' demographics, the location of the implants in the jaw, how long they were functional, and their overall health were obtained. The following measurements were taken: PD, crestal level bone loss (CBL), and plaque and gingival indices of peri-implant tissue. Interleukin-1, Galectine-1 and SuPAR levels in the Peri Implant tissue were assessed. A sample size calculation and statical analysis were carried out. The relationship between suPAR, galectin-1, and IL-1 was investigated using logistic regression analysis. Statistics were considered significant when p-values were less than 0.05. A total of 72 individuals with peri-implant problems were included (45 men and 27 women). 36 patients (23 men and 13 women) had healthy peri implant tissues, while 36 patients which includes 14 female and 22 males had PIM. Patients with peri implant complications showed a significantly more PISF volume (0.52 ±0.05 l) than those without (0.06 ±0.01 l) ($p< 0.001$). Peri implant problems were associated with higher levels of SuPAR which has p value < 0.01, galectin-1 which has p value < 0.01, and IL-1 which has p value < 0.01 PISF compared to those without. Peri implant crevicular fluid which has p value <0.001 and galectin-1 which has p value <0.001 levels were associated with PICF Interleukin -1 levels in patients who have PIM. PIM patients have higher levels of PD and IL-1, as well as PISF suPAR which has p value < 0.001 and galectin-1 which has p value < 0.05. He concluded that SuPAR, galectin, and IL-1 levels are higher in the PISF indicate that these proteins may play a role in the development of peri-implant inflammation and may serve as possible biomarkers for peri-implant disorders (Alshiddi et al., 2021).

Ali and colleagues quantified the levels of whole- suPAR and Tumor necrosis factor α in individuals with type II diabetes and those without diabetes, as well as assessment of periodontal clinic radiographic status. The study included patients with diabetes type II as well as those without diabetes. Each individual had their HbA1c levels tested. Four groups were formed. The patients diagnosed with inadequately managed type II diabetes, those with well-controlled type II diabetes, those with periodontitis, and those without periodontitis. Clinical and Radiographical periodontal parameters were evaluated, including GI, PI, PD mesial and distal MBL and CAL. TNF-alpha, suPAR, and total protein content (TPC) in saliva were all measured. The statistically significant difference was fixed at p value < 0.01. A number of 100 patients were present (25 in each group). Compared to groups 2-4, group 1 had significantly higher scores for GI which has p value $\leq$ 0.01, PI which has p value $\leq$ 0.01, CAL ($p \leq 0.01$), PD ($p \leq 0.01$), some of the missing teeth, and mesial and distal MBL. Group 3 had statistically significant higher PI, GI, PD score ,mesial and distal MBL score and has number of additional missing teeth compared to groups 2 and 4 ($p \leq 0.01$). In comparison to groups 2-4, patients in group 1 had markedly elevated levels of salivary TPC, suPAR, and TNF α a ($p \leq 0.01$). He found that patients with poorly controlled type-2 DM had poorer clinicoradiographic periodontal health and greater whole saliva levels of suPAR, TNF-a, and TPC than patients with well-controlled type-2 DM and non-diabetics (Ali et al., 2021).

Ali compared IL-1 and level of suPAR l in peri implant crevicular fluid from individuals who had prosthesis which was cement retained and screw retained prosthesis on implants. The study included individuals with both CR and SR implants. In addition to demographic data, records were examined for implant-related information such as implant geometry, torque while insertion, technique used while loading , retention technique, location of implant on jaw, length of function and depth of insertion . The following parameters were calculated: CBL, PD, modified PI, and modified BI. The levels of suPAR and IL-1 in PISF were measured. The correlations between clinico-radiographic factors, PISF IL-1, and suPAR were assessed, and statistical comparisons were made. Statistical significance was considered as $P < 0.05$. There was no difference between SR and CR devices in terms of clinical and radiological data. The amount of PISF cement retained prosthesis (0.22±0.004

l) and screw-retained (0.19±0.005 l) implants stayed the same. In conclusion, given strict oral hygiene, implants with CR or SR restorations are comparable in terms of clinico-radiographic status, with IL-1 and suPAR levels in the PISF falling within the normal range (Ali, 2023).

In 2023, Dewan and colleagues evaluated peri-implantitis in smokers and nonsmokers using PISF levels of suPAR and TNF-alpha. It included 60 male patients with peri-implantitis in total. Twenty smokers and twenty nonsmokers had peri-implantitis (Groups 1 and 2), while twenty nonsmokers did not (Group 3). Both demographic data and smoking-related characteristics were recorded. Some Indices were recorded such as PI and GI, PD, and crestal level of bone loss were among the peri-implant clinicoradiographic variables assessed. They examined the concentrations of suPAR and TNF-alpha in crevicular fluid samples collected surrounding implants. All parameters were statistically evaluated, and the sample size was estimated. The significance level was set at $P \leq 0.05$. Group 1 had significantly larger peri-implant PI, PD, mesial P value $\leq$ 0.01, and distal P value $\leq$ 0.01 CBLs compared to other groups (2, 3). Compared to Group 3, Groups 1 and 2 had significantly greater Peri Implant Crevicular Fluid volume, salivary soluble urokinase-type plasminogen activator receptor, and Tumor Necrosis Factor alpha levels. (Dewan et al., 2023).

Research Questions

Will suPAR levels in peri-implant crevicular fluid be an independent diagnostic and prognostic biomarker of peri-implantitis?

Research Objectives

The objectives of the proposed research are:

1. Analyse and compare PICF suPAR levels in healthy peri implant mucosa versus peri implant mucositis.
2. Assess and compare PICF suPAR levels among peri implant health and peri implantitis.
3. Assess and compare PICF suPAR levels between peri implant mucositis and peri implantitis.
4. Compare suPAR levels in PICF between healthy Peri implant mucosa, peri implant mucositis, and peri implantitis sites based on clinical association.

Proposed Hypothesis

SuPAR level in detected in PICF is a predictive indicator for peri-implant diseases.

Research Methodology

1. **Sources of the Data**

Participants will be selected from the outpatient department in the Department of Periodontics at the Karnavati School of Dentistry in Gandhinagar. The research protocol will be validated first by the Institutional Ethics Committee (IEC) and will adhere to the Declaration of Helsinki regarding the conduction of biomedical research that involves human participants.

2. **Study Type & Sample size calculation**

Type of study: Observational-cross-section

Sample size was determined using the following formula,

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 p_1(1-p_1) + p_2(1-p_2) (p_1 - p_2)^2$$

As there are three groups, each group consist of 29 samples at 95% Confidence interval and p value <0.05.

Therefore, a sum of 60 samples from 60 peri-implant sites will be categorized into three distinct groups.

- Healthy Peri implant tissue -Group A- 30 subjects
- Peri implant mucositis -Group B- 30 subjects
- Peri implantitis -Group C- 30 subjects

Group A

❋ *Criteria for healthy Peri-implant tissue* (Berglundh et al., 2018; Renvert et al., 2018)

a) No signs of inflammation.
b) No Bleeding on probing, a modified sulcus bleeding index has been proposed using a grading scale of the extent of bleeding at dental implants (Mombelli et al., 1987).
c) The amount of crestal bone loss that occurs after the first healing process should not be more then 2 mm.
d) Pocket depth ≤ 5 mm.

Group B

❋ *Criteria for Periimplant Mucositis* (Renvert et al., 2018)

a) Signs of inflammation
b) Presence of Bleeding on probing
c) Absence of further bone loss following initial healing, which should not be ≥2 mm.
d) Pocket depth ≤ 5 mm

Group C

❋ *Criteria for Periimplantitis* (Renvert et al., 2018)

a) Signs of inflammation

b) Presence of Bleeding on probing

c) ≥3 mm of bone loss on radiographs.

d) Pocket depth ≥6 mm

3. **Patient selection**

Inclusion criteria

i. Patients ≥ 30 years of age both male and female patients will be included

ii. Good general health.

iii. Healthy adjacent teeth.

Exclusion criteria

i. Use of anti-inflammatory therapy within the 3 months prior to the study.

ii. Tobacco in any form.

iii. Diabetes, cardiovascular, pulmonary, renal, hepatic, hematological, or metabolic bone diseases.

iv. Parturiency & Lactating Mother.

v. History of periodontal therapy, antibiotics, antiseptic 6 months prior to inclusion.

vi. Patients taking drugs such as cyclosporine A, calcium, bisphosphonates, steroids, vitamin A, or hormone replacement therapy (HRT) may experience a distinct progression of periodontal disease.

Participants in the study will be partially edentulous, and have had one or more endosseous implants to support a fixed prosthesis. All oral implants have been implanted for a minimum of 12 months and functionally loaded for a minimum of 6 months; they are now in the maintenance phase of oral implant therapy (Oringer et al., 1998).The sample processes will be thoroughly described to the patients, and their informed consent will be obtained.

4. **Clinical Parameters**

i. Pocket probing depth (PD) – Assessed from Gingival margin till base of the sulcus (Gargiulo et al., 1961)

ii. Clinical attachment level – Assessed from crown implant junction till base of the sulcus.

iii. Modified plaque index (Mombelli et al., 1987)

The surfaces examined are the four areas of the tooth i.e., the distal-facial, facial, mesial-facial surfaces and the entire lingual surfaces.

iv. Modified sulcus bleeding index (Mombelli et al., 1987)

Each of the four gingival areas of the tooth (distal-facial papilla, facial margin, mesial-facial papilla, and the entire lingual gingival margin) will be assessed for gingival inflammation and bleeding by running a periodontal probe along the soft tissue wall of the gingival crevice.

v. Suppuration: suppuration will be assessed as purulent discharge from gingival sulcus on probing or digital pressure along the gingiva of associated dental implant (Renvert et al., 2018).

vi. Radiographic evaluation: radiographic bone assessment will be calculated as follows (Abreu et al., 2007).

i. Bone Level (%) = 100 – D1 x 100/IH where,

IH - Implant height and,

D1 - distance from the most coronal portion of the osseous support to the implant apex as a reference

ii. Radiographic Bone Loss (%) = Final bone level (%) – Initial bone level (%)

All clinical parameters will be evaluated by UNC- 15 Periodontal Probe (Hu-Friedy) and will be checked by the same examiner.

5. **Peri-implant crevicular fluid sampling**

Prior to clinical recordings, samples of peri-implant crevicular fluid (PICF) will be collected to prevent contamination from blood and potential stimulation of PICF flow during measurements. A total of 2 µL of gingival crevicular fluid (GCF) will be collected using calibrated volumetric microcapillary pipettes with a volume range of 1 to 5µL. The sampling procedure include isolating that area using sterile cotton rollers, eliminating supragingival plaque, and air-drying the location to eliminate any contamination from plaque or saliva, and gently collecting the GCF from the entrance of the gingival sulcus without inserting the pipette into the crevice. Specimens contaminated with blood or saliva will be disposed off. The specimen will promptly be transferred to an Eppendorf tube filled with phosphate buffered solution and then frozen at a temperature of -80°C.. The assay will next be carried out according to the manufacturer guidelines using the suPAR ELISA test kit.

6. **Measurement of suPAR in PICF**

The amount of suPAR in PICF samples will be determined using an ELISA kit, as directed by the manufacturer.

7. **Statistical analysis**

The results will be tabulated and statistically analyzed using SPSS software (version 20, ©SPSS, Chicago, IL). The average and variability of the data will be supplied. If the samples exhibit a normal distribution, the analysis of variance (ANOVA) with a post-hoc Tukey test will be employed to evaluate the disparities across groups. Conversely, if the data is contrary to a normal distribution, the Kruskal-Wallis test with a post-hoc Bonferroni test will be utilized. Values are considered significant when the P value < 0.05.

Visible Research Outputs

SuPAR levels in PICF are beneficial for predicting long term disease susceptibility and prognosis, as well as economic viability.

References

Abreu, M. H., Bianchini, M. A., Magini, R. S., & Rösing, C. K. (2007). Clinical and radiographic evaluation of periodontal and peri-implant conditions in patients with implant-supported prosthesis. *Acta Odontol Latinoam AOL*, *20*(2), 87–95.

Ali, D. (2023). Levels of interleukin 1-beta and soluble urokinase plasminogen activation factor in peri-implant sulcular fluid of cement- and screw-retained dental implants. *Quintessence International (Berlin, Germany: 1985)*, *0*(0), 0. https://doi.org/10.3290/j.qi.b3877567

Ali, D., Qasem, S. S., & Baskaradoss, J. K. (2021). Periodontal Clinicoradiographic Status and Whole Saliva Soluble Urokinase Plasminogen Activation Receptor and Tumor Necrosis Factor Alpha Levels in Type-2 Diabetic and Non-diabetic Individuals. *Oral Health & Preventive Dentistry*, *19*(1), 481–488. https://doi.org/10.3290/j.ohpd.b2082019

Alshiddi, I. F., AlMubarak, A. M., Alqutub, M. N., Alqarawi, F. K., Alshahrani, F. A., Javed, F., Vohra, F., & Abduljabbar, T. (2021). Peri-implant Sulcular Fluid Galectin-1, Soluble Urokinase Plasminogen Activator Receptor and IL-1β Levels under Peri-implant Inflammatory Conditions. *Oral Health & Preventive Dentistry*, *19*(1), 503–510. https://doi.org/10.3290/j.ohpd.b2082081

Araujo, M. G., & Lindhe, J. (2018). Peri-implant health. *Journal of Periodontology*, *89 Suppl 1*, S249–S256. https://doi.org/10.1002/JPER.16-0424

Berglundh, T., Armitage, G., Araujo, M. G., Avila-Ortiz, G., Blanco, J., & Camargo, P. M. (2018). Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol*.

Berglundh, T., Lindhe, J., Ericsson, I., Marinello, C. P., Liljenberg, B., & Thomsen, P. (1991). The soft tissue barrier at implants and teeth. *Clin Oral Implants Res*, *Jun;2(2):81–90*.

Berglundh, T., Lindhe, J., Jonsson, K., & Ericsson, I. (1994). The topography of the vascular systems in the periodontal and peri-implant tissues in the dog. *J Clin Periodontol*, *Mar;21(3):189–93*.

Blasi, F., & Carmeliet, P. (2002). UPAR: a versatile signalling orchestrator. *Nat Rev Mol Cell Biol*, *Dec;3(12):932–43*.

Derks, J., & Tomasi, C. (2015). Peri-implant health and disease. A systematic review of current epidemiology. *J Clin Periodontol*, *Apr;42 Suppl 16:S158-171*.

Dewan, H., Robaian, A., Divakar, D. D., Hegde, S. M. R., Shankar, S. M., & Poojary, B. (2023). Levels of peri-implant sulcular fluid levels of soluble urokinase plasminogen activator receptor and TNF-α among cigarette smokers and non-smokers with peri-implantitis. *Technology and Health Care: Official Journal of the European Society for Engineering and Medicine*, *31*(1), 1–9. https://doi.org/10.3233/THC-213123

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*, 1149–1160.

Gargiulo, A. W., Wentz, F. M., & Orban, B. (1961). Dimensions and Relations of the Dentogingival Junction in Humans. *J Periodontol*, *32*(3), 261–267.

Güncü, G. N., Akman, A. C., Günday, S., Yamalık, N., & Berker, E. (2012). Effect of inflammation on cytokine levels and bone remodelling markers in peri-implant sulcus fluid: A preliminary report. *Cytokine*, *Aug;59(2):313–6*.

Güncü, G. N., Tözüm, T. F., Güncü, M. B., Yamalik, N., & Tümer, C. (2009). A 12-month evaluation of nitrite oxide metabolism around immediate and conventionally loaded dental implants. *Implant Dent*, *Feb;18(1):27–37*.

Hamad, S. A., & Mahmood, M. S. (2022). Assessment of Serum Levels of Soluble Urokinase Plasminogen Activator Receptor (suPAR) in Patients with Periodontitis and Atherosclerotic Cardiovascular Disease. *Journal of Research in Medical and Dental Science*, *10*(2), 719–723.

Heitz-Mayfield, L. J., & Salvi, G. E. (2018). Peri-implant mucositis. *J Clin Periodontol*, *45:S237–45*.

Huai, Q., Mazar, A. P., Kuo, A., Parry, G. C., Shaw, D. E., & Callahan, J. (2006). Structure of human urokinase plasminogen activator in complex with its receptor. *Science, 3;311(5761):656–9.*

Isola, G., Polizzi, A., Alibrandi, A., Williams, R. C., & Leonardi, R. (2021). Independent impact of periodontitis and cardiovascular disease on elevated soluble urokinase-type plasminogen activator receptor (suPAR) levels. *J Periodontol, 92*(6), 896–906.

Mombelli, A., Oosten, M. A., Schurch, E., & Land, N. P. (1987). The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol, Dec;2(4):145–51.*

Oringer, R. J., Palys, M. D., Iranmanesh, A., Fiorellini, J. P., Haffajee, A. D., & Socransky, S. S. (1998). C-Telopeptide pyridinoline cross-links (ICTP) and periodontal pathogens associated with endosseous oral implants. *Clin Oral Implants Res, Dec;9*(6), 365–373.

Ostergaard, C., Benfield, T., Lundgren, J. D., & Eugen-Olsen, J. (2004). Soluble urokinase receptor is elevated in cerebrospinal fluid from patients with purulent meningitis and is associated with fatal outcome. *Scand J Infect Dis, 36*(1), 14–19.

Pliyev, B. K., & Menshikov, M. Y. (2010). Release of the soluble urokinase-type plasminogen activator receptor (suPAR) by activated neutrophils in rheumatoid arthritis. *Inflammation, Feb;33(1):1–9.*

Ploug, M., Rønne, E., Behrendt, N., Jensen, A. L., Blasi, F., & Danø, K. (1991). Cellular receptor for urokinase plasminogen activator. Carboxyl-terminal processing and membrane anchoring by glycosyl-phosphatidylinositol. *J Biol Chem.*

Renvert, S., Persson, G. R., Pirih, F. Q., & Camargo, P. M. (2018). Peri-implant health, peri-implant mucositis, and peri-implantitis: Case definitions and diagnostic considerations. *Journal of Periodontology, 89 Suppl 1*, S304–S312. https://doi.org/10.1002/JPER.17-0588

Roldan, A. L., Cubellis, M. V., Masucci, M. T., Behrendt, N., Lund, L. R., & Danø, K. (1990). Cloning and expression of the receptor for human urokinase plasminogen activator, a central molecule in cell surface, plasmin dependent proteolysis. *EMBO J, Feb;9(2):467–74.*

Schwarz, F., Derks, J., Monje, A., & Wang, H.-L. (2018). Peri-implantitis. *J Periodontol.*

Senoo, T., Hattori, N., Tanimoto, T., Furonaka, M., Ishikawa, N., & Fujitaka, K. (2010). Suppression of plasminogen activator inhibitor-1 by RNA interference attenuates pulmonary fibrosis. *Thorax, Apr;65(4):334–40.*

Skottrup, P., Dahlén, G., Baelum, V., & López, R. (2018). Soluble urokinase-type plasminogen activator receptor is associated with signs of periodontitis in adolescents. *Eur J Oral Sci.*

Strimbu, K., & Tavel, J. A. (2010). *What are biomarkers? Curr Opin HIV AIDS* (Issue v;5(6):463–6).

Taşdemir, İ., Erbak Yılmaz, H., Narin, F., & Sağlam, M. (2020). Assessment of saliva and gingival crevicular fluid soluble urokinase plasminogen activator receptor (suPAR), galectin-1, and TNF-α levels in periodontal health and disease. *J Periodontal Res, Oct;55(5):622–30.*

Thunø, M., Macho, B., & Eugen-Olsen, J. (2009). SuPAR: the molecular crystal ball. *Dis Markers, 27*(3), 157–172.

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Periodontology, 89*(Suppl 1), S159-72.

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